Remarks

Status of the Claims

Claims 1-10 are currently pending. Claims 1 and 9 have been amended herein to more particularly point out the invention. Support for the amendment is found on page 6, line 20-page 7, line 1, and page 31, lines 12-16. New claim 11 has been added to more particularly point out the invention. Support for claim 11 is found in the specification on page 6, lines 9-19. No new matter has been added by these amendments.

Anticipation Rejection Under 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1-10 as allegedly anticipated by Blazar et al. (WO 95/34320, hereinafter Blazar). The Examiner alleges Blazar teaches the use of inhibitors, including those that bind both B7-1 and B7-2 to induce T cell unresponsiveness for bone marrow transplantation.

The standard required for finding anticipation under 35 U.S.C. § 102(b) is stated in MPEP § 2131. "'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)." Blazar does not meet this standard, and therefore, does not anticipate the claimed invention.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

In our response to the Office Action dated April 1, 2002, we argued that Blazar did not teach contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and recipient cells from the patient from about 1 to about 48 hours before being introduced to the patient. In response, the Office alleges that Blazar teaches saturating B7 with "inhibitors" such as hCTLA-4Ig and anti-LFA-1 for 3 hours, and thus Blazar meets the claim limitation, "from about 1 to about 48 hours," found in independent claims 1 and 9. (Claims 2-8 depend on claim 1. Claim 10 depends on claim 9.) The Examiner concludes that claims 1-10 are thus anticipated by Blazar. The conclusion, however, is mistaken.

The claims do not recite the limitation "inhibitors." Claims 1 and 9 recite "contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific for B7-2 . . . from about 1 to 48 hours" (emphasis added). hCTLA-4Ig is a CTLA-4 Ig fusion protein (Blazar, Abstract). It is not an immunoglobulin specific to either B7-1 or B7-2. Anti-LFA-1 is also not an immunoglobulin specific to B7-1, or an immunoglobulin specific for B7-2. The anti-LFA-1 antibody specifically recognizes LFA-1, a protein distinct from B7-1 or B7-2. LFA-1 is an integrin protein that binds ICAM-1, ICAM-2 and/or ICAM-3, whereas B7-1 and B7-2 bind to CD28 and CTLA4 surface receptors on T cells. (Blazar page 7, line 23 - page 8, line 18; page 2, lines 2-8).

Moreover, Blazar teaches a priming step of contacting donor and recipient cells for 2.5-4 days before the mixture is contacted with CTLA-4Ig and anti LFA-1. The instant claims recite "donor cells, the recipient cells, the immunoglobulin specific to B7-1 and the immunoglobulin specific to B7-2 are in contact for a period of time from about 1

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

to 48 hours," thus the instant claimed invention is distinct from Blazar. Because Blazar fails to teach every element of the claimed invention it cannot anticipate the claimed invention. Applicants respectfully request the withdrawal of this rejection.

Obviousness Rejection Under 35 U.S.C. § 103

Claims 1-10 stand rejected as being obvious in light of Blazar alone, or in combination with U.S. Patent No. 6,096,537 (hereinafter Chappel). The Office alleges the claimed invention is rendered obvious by Blazar because Blazar allegedly discloses a 3-hour in vitro incubation step with non-antibody B7 inhibitors and additionally discloses B7 specific antibodies administered in vivo. The Office further alleges the claimed invention is rendered obvious by Blazar in light of Chappel, which teaches masking antigens for 30 minutes to induce immunological non-responsiveness. Applicants submit the rejection is in error and respectfully request that it be withdrawn.

The Claimed Invention Is Not Prima Facie Obvious

MPEP § 2143 provides the standard required to establish a prima facie case of obviousness. "First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references combined) must teach or suggest all the claim limitations."

The PTO has not established that the claimed invention is prima facie obvious in light of the teachings of Blazar alone. The disclosure in Blazar alone would not provide

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

the skilled artisan with a reasonable expectation of success in attaining the claimed invention. Chappel adds nothing to cure this defect.

The reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The references must be considered as a whole and must suggest the desirability, and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP §2141. The Patent and Trademark Office (PTO) bears the burden of initially establishing a prima facie case of obviousness. MPEP § 2142.

The Invention Is Not Obvious In Light of Blazar Alone

The Office points to the same passage in Blazar discussed above regarding anticipation, in combination with the in vivo administration of B7-1 and B7-2 specific antibodies, to now allege that the claimed invention is obvious under 35 U.S.C. § 103. The Office alleges that a skilled artisan would have been motivated by Blazar to use the 3 hour in vitro hCTLA-4Ig and anti-LFA-1 incubation step disclosed in Blazar with the B7-1 and B7-2 specific antibodies of the claimed invention. Based on this reasoning the Office concludes the claimed invention is obvious. This conclusion lacks merit.

Blazar only uses the 3 hour incubation period cited by the Office, after a priming step of either 3 days or 2.5-4 days (see Blazar page 28, line 33-page 29, line 12). A priming step is not recited in the instant claims. Reading Blazar, a skilled artisan would find no reasonable expectation of success in eliminating this step. At best, eliminating the priming step was obvious to try. Obvious to try, however, is not the standard under

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

35 U.S.C. § 103. *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673, F.2d 894, 902 U.S.P.Q. 1673, 1680 (Fed. Cir. 1988).

Moreover, Blazar employed the 3 hour in vitro incubation period with only one B7 inhibitor, i.e. CTLA-4Ig. In various experiments it was combined with a second agent that inhibited T cell function by inhibiting pathways/mechanisms that are distinct from the B7/CD28 co-stimulatory pathway. Blazar's second agent, instead, focused on the IL-2 pathway or inhibition of T cell adhesion to antigen presenting cells with anti-LFA-1. In other cases, the CTLA-4Ig was administered alone. The in vitro regimen was sometimes followed with a continued in vivo dose of one or more agents. The results obtained showed the best survival rates were obtained when 2 pathways/mechanisms were targeted for disruption *(e.g.,* the B7 costimulatory pathway and either the IL-2 pathway or the adhesion mechanism). The mice that received only CTLA-4Ig did not fare as well as the mice that were treated with two distinct agents (see Blazar Experiments 1-3, pages 29-31 and Figures 1, 5, and 7). Blazar, therefore, teaches that an in vitro incubation prior to transplant requires a regimen that targets at least two distinct pathways/mechanisms. Thus, Blazar teaches away from performing an in vitro incubation step targeting only one pathway. See *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986).

Antibodies to B7-1 and B7-2 both target the same pathway, i.e. the B7/CD28 co-stimulatory pathway. A skilled artisan would thus find no reasonable expectation of success in Blazar to use B7-1 and B7-2 specific antibodies in an ex vivo regimen to

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

induce tolerance. Blazar does not teach why this regimen would be desirable. The claimed invention therefore cannot be obvious in light of Blazar alone.

Blazar Combined With Chappel

The Examiner alleges that the disclosure in Chappel of a thirty minute in vitro incubation step of donor cells with a masking agent when combined with Blazar renders the claimed invention obvious. This allegation is not supported by the cited references.

The invention in Chappel is clearly distinct from the claimed invention. Chappel does not teach inhibiting the B7/CD28 pathway. Chappel does not teach or suggest the ex vivo application of antibodies to B7-1 or B7-2 in a method of transplanting cells. Instead, Chappel teaches masking LFA-1, MHC I, or MHC II. None of the molecules disclosed by Chappel activate T cells via the B7/CD28 co-stimulatory pathway. Thus, Chappel merely suggests the use of a 30 minute in vitro incubation step with reagents that target molecules distinct from the claimed invention. Nonetheless, the Office suggests the 30 minute incubation period disclosed in Chappel could be combined with the immunomodulatory methods disclosed in Blazar and thus, would render the claimed invention obvious. But no reasonable expectation of success existed in combining the 30 minute incubation step disclosed in Chappel with Blazar because Chappel did not target the B7 pathway and Blazar discloses effective immunomodulation requires a lengthy priming step when the B7 pathway is targeted ex vivo. There is nothing in either Chappel or Blazar to suggest that targeting the B7 pathway with a 30 minute ex vivo incubation period would be successful. The Office is reminded that the reasonable expectation of success must be found in the references and not in the Applicants

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

disclosure. *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The Office has failed to establish a prima facie case of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-10 under 35 U.S.C. §103.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this filing and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: June 26, 2003

By: E Stewart Mittler
E. Stewart Mittler
Reg. No. 50,316

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX OF AMENDMENTS

VERSION WITH MARKINGS TO SHOW CHANGES

Please amend the claims as follows:

1. (Twice Amended) A method for transplanting cells to a patient in need thereof, comprising:

a) obtaining cells from a donor,

b) obtaining recipient cells from the patient;

c) contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and recipient cells from the patient such that the donor cells, the recipient cells, the immunoglobulin specific to B7-1, and the immunoglobulin specific to B7-2 are in contact for a period of time from about 1 to about 48 hours, thereby obtaining a mixture, and

d) introducing the mixture after the contacting step of c) to the patient.

9. (Twice Amended) A method for transplanting cells to a patent in need thereof, comprising:

a) obtaining cells from a donor,

b) obtaining a tissue, an organ, or recipient cells from the patient,

c) contacting the donor cells with an immunoglobulin specific to B7-1, an immunoglobulin specific to B7-2, and the tissue, the organ, or the recipient cells that express MHC Class I antigen, B7-1 and B7-2 molecules, such that the donor cells, the tissue organ or recipient cells, the immunoglobulin specific to B7-1, and the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

immunoglobulin specific to B7-2 are in contact for a period of time from about 1 to about 48 hours, thereby obtaining a mixture, and

d) introducing the mixture after the contacting step of c) to the patient.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com